

Retrospective Study

Secondary endoscopic submucosal dissection for locally recurrent or incompletely resected gastric neoplasms

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Author contributions: All authors performed the research; Jung DH contributed to manuscript writing, performing procedures, and data analysis; Youn YH contributed to manuscript writing, conception and design, performing procedures, and data analysis; Kim JH, Park JJ, and Park H contributed to writing the manuscript and performing procedures.

Supported by Basic Science Research Program through the National Research Foundation of Korea(NRF) funded by the Ministry of Science and ICT(NRF-2015R1C1A1A01054352).

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of the Gangnam Severance Hospital.

Conflict-of-interest statement: All authors declare no conflicts-of-interest related to this article.

Data sharing statement: No additional data are available.

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Manuscript source: Unsolicited manuscript

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Received: June 11, 2018

Peer-review started: June 11, 2018

First decision: July 6, 2018

Revised: July 31, 2018

Accepted: August 1, 2018

Article in press: August 1, 2018

Published online: September 7, 2018

Abstract

AIM

To investigate the feasibility and safety of secondary endoscopic submucosal dissection (ESD) for residual or locally recurrent gastric tumors.

METHODS

Between 2010 and 2017, 1623 consecutive patients underwent ESD for gastric neoplasms at a single tertiary referral center. Among these, 28 patients underwent secondary ESD for a residual or locally recurrent tumor. Our analysis compared clinicopathologic factors between primary ESD and secondary ESD groups.

RESULTS

The en bloc resection and curative rate of resection of secondary ESD were 92.9% and 89.3%, respectively. The average procedure time of secondary ESD was significantly longer than primary ESD (78.2 min *vs* 55.1 min, $P = 0.004$), and the adverse events rate was not significantly different but trended slightly higher in the secondary ESD group compared to the primary ESD group (10.7% *vs* 3.8%, $P = 0.095$). Patients who received secondary ESD had favorable outcomes without severe adverse events. During a mean follow-

up period, no local recurrence occurred in patients who received secondary ESD.

CONCLUSION

Secondary ESD of residual or locally recurrent gastric tumors appears to be a feasible and curative treatment though it requires greater technical efficiency and longer procedure time.

Key words: Secondary endoscopic submucosal dissection; Endoscopic submucosal dissection; Gastric neoplasms; Residual tumors; Recurrent tumors

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Core tip: Although secondary endoscopic submucosal dissection (ESD) is technically demanding, it can be applied to residual or recurrent tumors. We categorized secondary ESD into three groups according to the surgical strategy and analyzed them. There is no consensus on the timing of salvage ESD. This is the first study to report the feasibility and safety of secondary ESD according to the timing of ESD. Although secondary ESD requires greater technical efficiency and a longer procedure time, secondary ESD of residual or locally recurrent gastric tumors appears to be a feasible and curative treatment.

Jung DH, Youn YH, Kim JH, Park JJ, Park H. Secondary endoscopic submucosal dissection for locally recurrent or incompletely resected gastric neoplasms. *World J Gastroenterol* 2018; 24(33): 3776-3785 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v24/i33/3776.htm> DOI: <http://dx.doi.org/10.3748/wjg.v24.i33.3776>

INTRODUCTION

Endoscopic submucosal dissection (ESD) technique has evolved, and various lesions can now be treated with ESD, regardless of their size and site, including ulcer scars with severe fibrosis^[1,2]. To achieve curative resection, it is very important to accurately predict the margin of neoplasm before ESD. Therefore, chromoendoscopy, magnifying endoscopy, and magnifying image-enhanced endoscopy are widely used to determine the appropriate lesion margin^[3,4]. However, despite these efforts, the positive lateral margins of a neoplasm can still occur after ESD. According to the Japanese gastric cancer treatment guidelines, surgical resection should be performed after non-curative resection of early gastric cancer^[5]. However, for patients with differentiated carcinoma in which the positive lateral margin is the only non-curative factor, secondary ESD can be performed given the low risk of lymph node metastasis in such cases.

Primary ESD is a relatively established technique that dissects along the loose submucosal layer. However,

secondary ESD is difficult because the submucosal layer is eliminated by the previous endoscopic resection and is replaced with fibrosis. In patients who have positive lateral margin after primary ESD, early secondary ESD is performed within a few days. This can be technically difficult because the orientation of the residual lesion might be confusing and development of submucosal fibrosis may have begun^[6]. Late secondary ESD is performed a few months after the primary ESD and is also technically demanding because of severe submucosal fibrosis. Until recently, there have only been a few reports of secondary ESD for residual or locally recurrent tumors^[6-8]. Therefore, this study aimed to investigate the feasibility and safety of secondary ESD procedures for residual or locally recurrent gastric neoplasms.

MATERIALS AND METHODS

Patients

Between January 2010 and February 2017, 1623 consecutive patients underwent gastric ESD for gastric neoplasms at Gangnam Severance Hospital in Seoul, Korea. Among these, 28 patients received secondary ESD for residual or locally recurrent tumors. We compared clinicopathologic factors between secondary ESD (28 patients) and primary ESD (1595 patients). The prospectively collected database of ESD and medical records were then reviewed and analyzed retrospectively to determine the feasibility and safety of ESD for residual or locally recurrent tumors. The Institutional Review Board (IRB) of Gangnam Severance Hospitals approved this study.

ESD procedure

Procedures were primarily performed using one or two ESD knives, including a DualKnife (Olympus Co., Tokyo, Japan), FlexKnife (Olympus Co., Tokyo, Japan), HookKnife (Olympus Co., Tokyo, Japan), and/or an insulated-tip knife (Olympus Co., Tokyo, Japan). Following circumferential marking (*via* argon plasma coagulation), a mixture of indigo carmine, epinephrine, and 10% glycerol (Cerol; JW Pharmaceutical Co, Seoul, South Korea) was used to inject the submucosa. The mucosa surrounding each lesion was then incised and dissection of the submucosal layer ensued. Hemostasis during ESD and ablation of visible vessels at the post-ESD ulcer site were achieved using hemostatic forceps (Coagrasper; Olympus Co, Tokyo, Japan). For the electrosurgical unit, the VIO300D (ERBE, Tuebingen, Germany) was used. Mucosal incision was performed using the Endocut I current (effect 2, cut duration 4, interval 3), and submucosal dissection was carried out with the swift coagulation current (effect 3, 40 W). The visible vessels were ablated using the soft coagulation current (effect 3, 60 W).

Secondary ESD procedure

In this study, secondary ESD refers to an additional ESD procedure for residual or locally recurrent tumors.

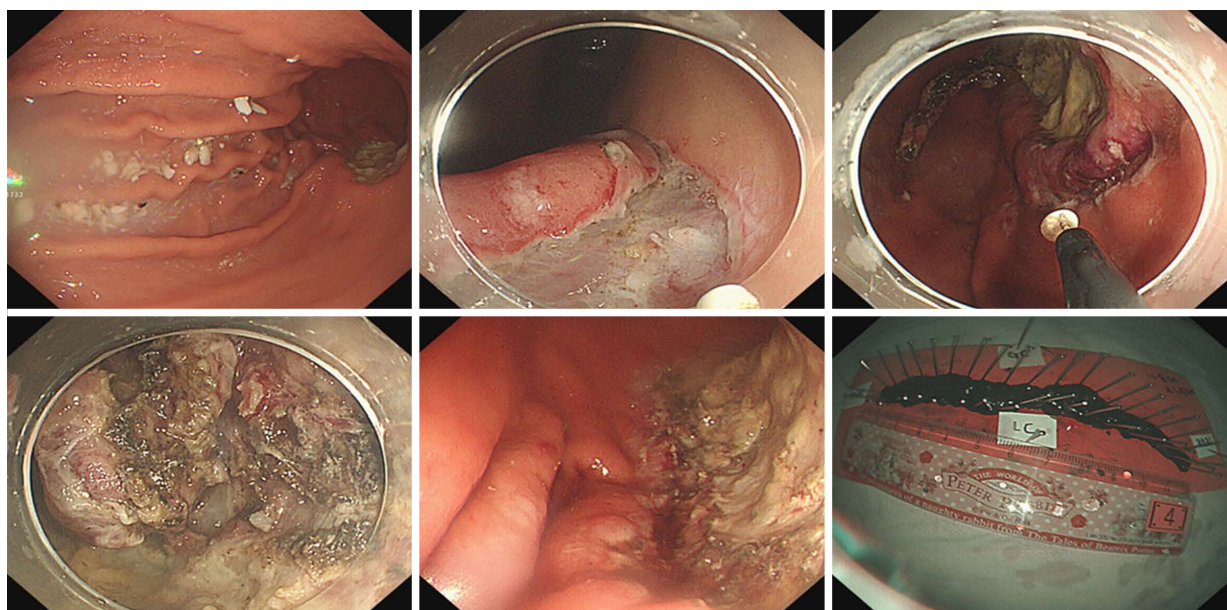


Figure 1 Case of early salvage endoscopic submucosal dissection. A 52 year old female patient was diagnosed with a 6 cm early gastric cancer on the posterior wall of the lower body. The primary ESD procedure was performed, and en bloc resection was achieved. The pathology report indicated the positive lateral margin. Early salvage ESD was performed after histological confirmation of positive lateral margins of the initial ESD specimen. ESD: Endoscopic submucosal dissection.

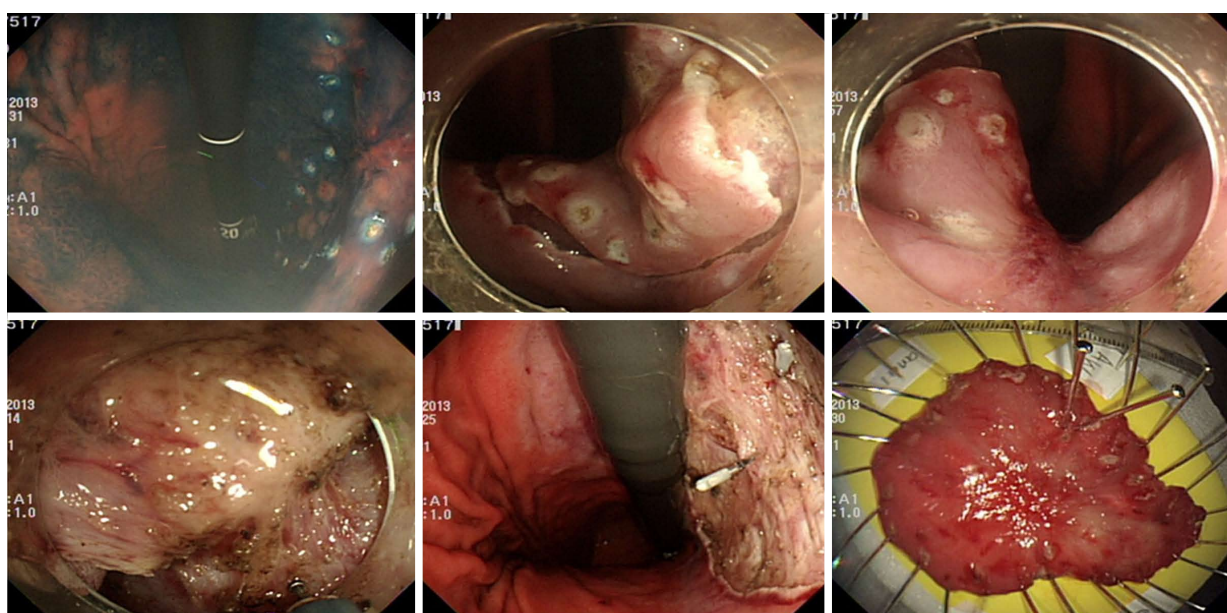


Figure 2 Case of late salvage endoscopic submucosal dissection. A 52 year old male patient was diagnosed with a 3 cm early gastric cancer on the posterior wall of the lower body. The primary ESD procedure was performed, and piecemeal resection was done incompletely due to severe bleeding and adhesion. Late salvage ESD was performed after complete healing of the artificial ulcer caused by the primary ESD. ESD: Endoscopic submucosal dissection.

Early salvage ESD was performed immediately after histological confirmation of positive lateral margins of the initial ESD specimen (Figure 1). Late salvage ESD was prescribed when the positive lateral margin was histologically confirmed after the initial ESD, and was performed after complete healing of the artificial ulcer caused by the initial ESD (Figure 2). Late secondary ESD was performed when local recurrence was proven histologically during the follow-up period after initially curative primary ESD (Figure 3). The general sequence

of early or late salvage and late secondary ESD were similar to that of the primary ESD. However, sodium hyaluronate (LG Life Science Co., Seoul, South Korea) was frequently used as a submucosal injection material to overcome non-lifting signs induced by ulceration and fibrosis of the submucosal layer caused by the primary ESD^[9]. In general, a non-insulated knife was used for dissecting fibrotic areas that were not lifted due to fibrosis. Additionally, to achieve an appropriate angle for a dissecting view of the submucosa in fibrotic area,

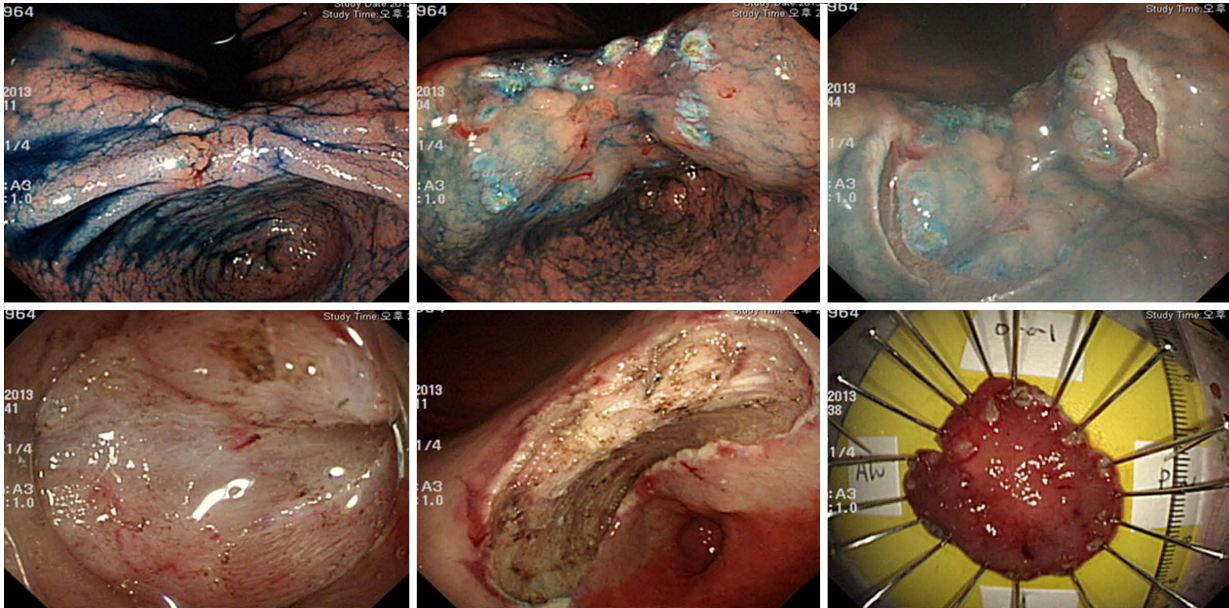


Figure 3 Case of late secondary endoscopic submucosal dissection. A 61 year old male patient was diagnosed with a 1.7 cm high grade dysplasia on the lesser curvature of the angle. The primary ESD procedure was performed, and en bloc resection was achieved. The local recurrence was shown five years after initial curative primary ESD. Late secondary ESD was performed. ESD: Endoscopic submucosal dissection.

the submucosal dissection was initiated in a non-fibrotic area of sufficient distance from the fibrotic area.

Histopathological evaluation of tumors

En bloc resection was defined as a tumor that was removed whole as a single piece. Curative resection was defined as expanded indications according to the Japanese gastric cancer treatment guidelines^[5]. According to the Japanese gastric cancer treatment guidelines, the expanded indications for curative endoscopic resection (ER) were en bloc resection, negative lateral and vertical margins, no lymphovascular invasion (LVI) and one of the following: (1) Tumor size > 2 cm, differentiated type, mucosa, and ulcer (-); (2) tumor size ≤ 3 cm, differentiated type, mucosa, and ulcer (+); (3) tumor size ≤ 2 cm, undifferentiated type, mucosa, and ulcer (-); or (4) tumor size ≤ 3 cm, differentiated type, and submucosa1 (SM1, < 500 μm from the muscularis mucosa).

Statistical analysis

Comparison of clinicopathologic factors between primary ESD and secondary ESD was performed using the chi-square test and Fisher's exact test. The Student's *t*-test was used for intergroup comparison of non-categorical variables. The accepted significance level was a *P* value < 0.05. All statistical analyses were performed using the software SPSS version 12.0 for Windows (SPSS Inc., Chicago, IL, United States).

RESULTS

Demographic and clinicopathologic characteristics

Among 1623 patients, 1595 patients received primary

ESD and 28 patients underwent secondary ESD. Six of these patients (21.4%) and eight of these patients (28.6%) underwent early and late salvage ESD for residual lesions, respectively, while fourteen of these patients (50.0%) underwent late secondary ESD for locally recurrent lesions. Baseline characteristics of the gastric lesions treated by ESD are shown in Table 1. There were significantly more depressed macroscopic lesions in the secondary ESD group and there were no significant differences in lesion location or size between the two groups. We investigated the initial lesion corresponding to secondary ESD. The initial lesions corresponding to secondary ESD were dysplasia in 13 patients, and carcinoma in 15 patients. A total of 15 patients with carcinoma had mucosal cancer without lymphovascular invasion.

Procedure outcomes

When we compared the procedure outcomes of the 1595 patients in the primary ESD group and the 28 patients in the secondary ESD group, the resected specimen size in the secondary ESD group was significantly larger than that of the primary ESD group, though the lesion size of two groups was not different. Next, significant differences in procedure outcomes were identified by comparing the primary ESD group and the secondary ESD group (Table 2). Patients in the secondary ESD group had a longer mean ESD procedure time than patients in the primary ESD group (78.2 min vs 55.1 min, *P* = 0.004). Additionally, the dissection times for the secondary ESD group were significantly longer than that of the primary ESD group (63.4 min vs 36.7 min, *P* < 0.001). Furthermore, the dissection speed was significantly lower in the secondary ESD group than in the primary ESD

Table 1 Baseline characteristics

Characteristics	ESD (<i>n</i> = 1595, %)	Secondary ESD (<i>n</i> = 28, %)	<i>P</i> value
Gender			0.836
Male	1117 (70.0)	19 (67.9)	
Female	478 (30.0)	9 (32.1)	
Age [yr, mean (SD)]	64.8 (10.4)	63.5 (9.2)	0.528
Lesion location			0.217
Upper	127 (8.0)	3 (11.1)	
Middle	633 (39.7)	15 (53.6)	
Lower	835 (52.4)	10 (35.7)	
Multiplicity	250 (15.7)	2 (7.1)	0.296
Lesion size [mm, mean (SD)]	17.4 (12.8)	16.4 (13.2)	0.664
Macroscopic type			< 0.001
Elevated	674 (42.3)	7 (25.0)	
Flat	685 (42.9)	9 (32.1)	
Depressed	236 (14.8)	12 (42.9)	
WHO classification			< 0.001
Low grade dysplasia	610 (38.2)	8 (28.6)	
High grade dysplasia	221 (13.9)	4 (14.3)	
Well differentiated	356 (22.3)	4 (14.3)	
Moderately differentiated	268 (16.8)	7 (25.0)	
Poorly differentiated	76 (4.8)	3 (10.7)	
Signet ring cell carcinoma	64 (4.0)	0 (0.0)	
No residual lesion	0 (0.0)	2 (7.1)	
Depth of invasion			< 0.001
Dysplasia	831 (52.1)	12 (42.9)	
Mucosal cancer	609 (38.2)	14 (50.0)	
Submucosal cancer	155 (9.7)	0 (0.0)	
No residual lesion	0 (0.0)	2 (7.1)	
LVI			1.000
No	1546 (96.9)	28 (100.0)	
Yes	49 (3.1)	0 (0.0)	
Lateral margin			0.381
Negative	1521 (95.4)	26 (92.9)	
Positive	74 (4.6)	2 (7.1)	
Vertical margin			0.615
Negative	1542 (96.7)	27 (96.4)	
Positive	53 (3.3)	1 (3.6)	

ESD: Endoscopic submucosal dissection; LVI: Lymphovascular invasion.

Table 2 Comparison of procedural outcomes and oncologic outcomes between the primary endoscopic submucosal dissection group and secondary endoscopic submucosal dissection group

	ESD (<i>n</i> = 1595, %)	Secondary ESD (<i>n</i> = 28, %)	<i>P</i> value
Lesion size [mm, mean (SD)]	17.4 (12.8)	16.4 (13.2)	0.664
Specimen size [mm, mean (SD)]	38.1 (14.6)	47.8 (19.6)	0.001
Whole procedure time [min, mean (SD)]	55.1 (41.5)	78.2 (38.0)	0.004
Dissection time [min, mean (SD)]	36.7 (34.7)	63.4 (38.0)	< 0.001
Dissection speed [mm ² /min, mean (SD)]	38.7 (32.8)	22.1 (12.7)	< 0.001
Complication	61 (3.8)	3 (10.7)	0.095
Perforation	37 (2.3)	0 (0.0)	
Bleeding	15 (0.9)	1 (3.6)	
Aspiration pneumonia	13 (0.8)	2 (7.1)	
Hospital stay [d, mean (SD)]	3.6 (3.2)	3.9 (2.5)	0.639
En bloc resection	1574 (98.7)	26 (92.9)	0.058
Curative resection	1383 (86.7)	25 (89.3)	1.000
Additive salvage treatment	104 (6.5)	3 (10.7)	0.425
Additive surgery	85 (5.3)	2 (7.1)	
Redo ESD	16 (1.0)	1 (3.6)	
Argon plasma coagulation	3 (0.2)	0 (0.0)	

ESD: Endoscopic submucosal dissection.

Table 3 Clinicopathologic characteristics according to surgical strategy

Characteristics	Early salvage ESD (<i>n</i> = 6, %)	Late salvage ESD (<i>n</i> = 8, %)	Late secondary ESD (<i>n</i> = 14, %)	<i>P</i> value
Gender				0.909
Male	4 (66.7)	5 (62.5)	10 (71.4)	
Female	2 (33.3)	3 (37.5)	4 (28.6)	
Age [yr, mean (SD)]	65.4 (10.8)	61.6 (7.3)	63.8 (9.9)	0.749
Lesion location				0.255
Upper	2 (33.3)	0 (0.0)	1 (7.1)	
Middle	2 (33.3)	4 (50.0)	9 (64.3)	
Lower	2 (33.3)	4 (50.0)	4 (28.6)	
Multiplicity	0 (0.0)	1 (12.5)	1 (7.1)	0.668
Lesion size [mm, mean (SD)]	19.8 (22.4)	13.6 (10.9)	16.4 (9.8)	0.701
Initial method				0.341
EMR	0 (0.0)	0 (0.0)	2 (14.3)	
ESD	6 (100.0)	8 (100.0)	12 (85.7)	
Macroscopic type				0.014
Elevated	0 (0.0)	0 (0.0)	7 (50.0)	
Flat	4 (66.7)	2 (25.0)	3 (21.4)	
Depressed	2 (33.3)	6 (75.0)	4 (28.6)	
WHO classification				0.081
Low grade dysplasia	2 (33.3)	3 (37.5)	3 (21.4)	
High grade dysplasia	0 (0.0)	1 (12.5)	3 (21.4)	
Well differentiated	1 (16.7)	0 (0.0)	3 (21.4)	
Moderately differentiated	1 (16.7)	4 (50.0)	2 (14.3)	
Poorly differentiated	0 (0.0)	0 (0.0)	3 (21.4)	
Signet ring cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	
No residual lesion	2 (33.3)	0 (0.0)	0 (0.0)	
Depth of invasion				0.090
Dysplasia	2 (33.3)	4 (50.0)	6 (42.9)	
Mucosal cancer	2 (33.3)	4 (50.0)	8 (57.1)	
Submucosal cancer	0 (0.0)	0 (0.0)	0 (0.0)	
No residual lesion	2 (33.3)	0 (0.0)	0 (0.0)	
LVI				1.000
No	6 (100.0)	8 (100.0)	14 (100.0)	
Yes	0 (0.0)	0 (0.0)	0 (0.0)	
Lateral margin				0.341
Negative	6 (100.0)	8 (100.0)	12 (85.7)	
Positive	0 (0.0)	0 (0.0)	2 (14.3)	
Vertical margin				0.617
Negative	6 (100.0)	8 (100.0)	13 (92.9)	
Positive	0 (0.0)	0 (0.0)	1 (7.1)	

EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection; LVI: Lymphovascular invasion.

group (22.1 mm²/min vs 38.7 mm²/min, *P* < 0.001). The adverse events rate in the secondary ESD group was not significantly different but trended slightly higher than that in the primary ESD group (10.7% vs 3.8%, *P* = 0.095). There were no perforations in the secondary ESD group.

Oncologic outcomes

The en bloc resection and curative rates of resection of secondary ESD were 92.9% and 89.3%, respectively. These rates were comparable with those of primary ESD, which had an en bloc resection rate of 98.7% and a curative resection rate of 86.7% (Table 2). Three patients in the secondary ESD group had additive salvage treatments due to a positive lateral margin (*n* = 2) and other synchronous lesions that had vertical margin involvement after secondary ESD (*n* = 1). One patient in the secondary ESD group showed a positive vertical margin with a very focal extension of dysplasia. This patient was 75 years old and decided to be observed

and was followed up closely. During follow-up, one patient who received secondary ESD presented with metachronous recurrence 25 months after secondary ESD. We evaluated the outcomes according to an institutional learning curve based upon the initial phase and the late phase of the study period. The en bloc resection rate was not significantly different (initial phase vs late phase, 98.4% vs 98.8%, *P* = 0.533). Curative resection rate was significantly lower in initial phase vs late phase (84.6% vs 88.8%, *P* = 0.013). When we evaluated the outcomes in the secondary ESD group, the en bloc and curative resection rates were not statistically different (initial phase vs late phase, 100% vs 88.2%, *P* = 0.505 and 90.9 % vs 88.2%, *P* = 1.000, respectively).

Subgroup analysis according to surgical strategy

We categorized secondary ESD into three groups according to the surgical strategy (early salvage, late salvage, or late secondary ESD) (Table 3). The median interval times from the primary ESD to the secondary

Table 4 Comparison of procedural outcomes and oncologic outcomes according to surgical strategy

	Early salvage ESD (<i>n</i> = 6, %)	Late salvage ESD (<i>n</i> = 8, %)	Late secondary ESD (<i>n</i> = 14, %)	<i>P</i> value
Lesion size [mm, mean (SD)]	19.8 (22.4)	13.6 (10.9)	16.4 (9.8)	0.701
Specimen size [mm, mean (SD)]	63.0 (33.0)	46.4 (11.6)	42.1 (12.8)	0.084
Whole procedure time [min, mean (SD)]	81.7 (48.5)	85.9 (24.3)	72.3 (41.1)	0.714
Dissection time [min, mean (SD)]	73.2 (46.8)	73.0 (23.4)	53.8 (40.7)	0.421
Dissection speed [mm ² /min, mean (SD)]	19.4 (6.8)	19.0 (7.5)	24.9 (12.7)	0.512
Method				0.341
ESD only	6 (100.0)	8 (100.0)	12 (85.7)	
ESD plus snaring	0 (0.0)	0 (0.0)	2 (14.3)	
Complication	0 (0.0)	1 (12.5)	2 (14.3)	0.627
Perforation	0 (0.0)	0 (0.0)	0 (0.0)	
Bleeding	0 (0.0)	0 (0.0)	1 (7.1)	
Aspiration pneumonia	0 (0.0)	1 (12.5)	1 (7.1)	
Hospital stay [d, mean (SD)]	7.2 (2.9)	3.0 (1.8)	3.0 (1.2)	< 0.001
Median interval [d, mean (SD)]	6.5 (3.1)	129.0 (133.6)	712.8 (546.5)	0.001
En bloc resection	6 (100.0)	8 (100.0)	12 (85.7)	0.341
Curative resection	6 (100.0)	8 (100.0)	11 (78.6)	0.186
Additive treatment	0 (0.0)	0 (0.0)	3 (21.4)	0.186
Additive surgery	0 (0.0)	0 (0.0)	2 (14.3)	
Redo ESD	0 (0.0)	0 (0.0)	1 (7.1)	

ESD: Endoscopic submucosal dissection.

ESD were 6.5, 129.0, and 712.8 d in patients who received early salvage, late salvage, or late secondary ESD, respectively. Hospital stay was significantly longer in early salvage ESD group compared with late salvage and late secondary ESD groups (7.2 d vs 3.0 d and 3.0 d, $P \leq 0.001$). There was no other significant difference in procedure outcomes among the three groups (Table 4). The en bloc and curative resection rates of early and late salvage groups were both 100%. However, the en bloc and curative resection rates of the late secondary ESD group tended to be lower than that of the other groups (Table 4).

DISCUSSION

ESD is now widely performed for gastric neoplasms and has favorable outcomes. However, the incomplete resection rate of ESD is 2.2% to 26.3%^[10-21] and the local recurrence rate after ESD is 0% to 3%^[15,16,22-24]. Therefore, the management of residual or locally recurrent gastric neoplasms after ESD continues to be problematic. Secondary ESD for a locally recurrent tumor is difficult to perform due to severe fibrosis and ulcer scar formation, and there are few published reports about secondary ESD for residual or locally recurrent gastric neoplasms. Bae *et al*^[6] reported a total of 16 early secondary ESD cases in which the curative resection rate was 93.8% (15/16). Therefore, they asserted that early secondary ESD was a feasible and useful treatment in patients with a positive lateral margin. Additionally, secondary ESD was also determined to be an effective treatment for locally recurrent lesions after endoscopic mucosal resection (EMR)^[7]. Oka *et al*^[7] reported that the complete resection rate of ESD for a residual or locally recurrent lesion is 93.3% (14/15). Therefore,

they suggested that secondary ESD was an effective and minimally invasive procedure for patients with residual or local recurrent tumors after EMR.

Secondary ESD is technically difficult due to the severe fibrosis and scar formation that results from primary ESD^[25]. In this study, the mean procedure time and dissection time of secondary ESD was longer than that for primary ESD. In addition, the dissection speed was lower in the secondary ESD group than in the primary ESD group, while the adverse events rate of secondary ESD was slightly higher than that of primary ESD. That is, secondary ESD is associated with a greater technical difficulty, longer procedure time, and increased incidence of adverse events. However, in this study, bleeding after secondary ESD was managed endoscopically, without the need for further emergent operation; aspiration pneumonia was treated with antibiotics and conservative care. The aspiration pneumonia occurred in 15 (0.9%) patients. The procedure time was longer in patients with aspiration pneumonia than others (83.3 min vs 55.1 min, $P = 0.125$). However, the difference was not statistically significant. Although many endoscopists worry that submucosal fibrosis might cause perforation, in this study, there were no perforations reported in the secondary ESD group. We suspected that deep excavation by benign peptic ulcers would not preserve the muscle layer. However, the artificial ulcer caused by ESD was contracted, preserving the muscle layer, which was thicker than before ESD. Therefore, this observation may explain the rarity of perforation. Primary ESD procedures in this study were performed by one of five ESD endoscopists. Two of them were fully skilled experts (YYH, far more than a thousand cases of ESD experience; KJH, more than five hundreds cases of ESD experience) and the other three were less-

skilled ESD endoscopists whose ESD experience were less than a hundred cases. However, secondary ESD in this study was exclusively performed only by the two fully skilled ESD experts (YYH and KJH). That might be a reason why the outcomes of the secondary ESD group were relatively good despite the technical difficulty.

ESD has multiple advantages compared to other treatment options for residual or locally recurrent tumors, such as gastrectomy and additional endoscopic treatment. Compared to gastrectomy, ESD offers improved quality of life, decreased morbidity, longer length of recovery, and lower healthcare costs. It also has advantages over other endoscopic treatments, such as argon plasma coagulation, including a high chance of en bloc resection, which allows for complete histologic assessment. Therefore, the application of secondary ESD for residual or locally recurrent tumors is an important treatment consideration.

When we categorized secondary ESD according to the time interval from primary ESD, the main difference between early secondary ESD and late secondary ESD was scar formation. Early secondary ESD is performed while the ESD ulcer is still open, therefore, there is minimal fibrosis. However, by the time late secondary ESD is performed, the ulcer has healed with severe fibrosis^[26]. In this study, we compared three groups: early salvage ESD, late salvage ESD, and late secondary ESD, and hospital stay of the early salvage ESD group was the longest. This difference was due to many patients in the early salvage ESD group that underwent primary and secondary ESD successively during a single hospitalization. There was no other significant difference in procedure outcomes regarding the whole procedure time, dissection time, and dissection speed among the three groups. Although the late salvage ESD and late secondary ESD groups had severe fibrosis and scar formations, no perforations occurred.

According to this study, secondary ESD for residual or locally recurrent tumors is a safe, minimally invasive, and effective treatment. However, secondary ESD should be performed by an experienced endoscopist with precautions, including the appropriate electrosurgical knife, the appropriate dissection depth, and the careful gradual dissection of the severe fibrotic tissue along the plane of the deep submucosa or superficial proper muscle. Furthermore, the surrounding non-fibrotic tissue should first be dissected sufficiently to make a flap of the specimen and directly visualize the plane of the submucosa from the non-lifting fibrotic area to the fibrotic area^[27,28]. Therefore, in this study, we found that the specimen size of the secondary ESD group was significantly larger than the primary ESD group. In addition, one recommendation for dissecting the fibrotic area is to dissect deeply along the surface of the muscle fiber because the ESD ulcer scar has an intact muscle layer.

Correct diagnosis of the depth of invasion of residual or locally recurrent tumors is often difficult

due to scar formation after ESD. Therefore, residual or locally recurrent tumors with submucosal invasion are sometimes misdiagnosed as mucosal cancer^[29]. In this study, the depth of invasion of all secondary ESD was within the mucosa.

In previous reports, the curative resection rate for residual gastric neoplasms was 92% to 100%^[6,26,30] and curative resection rate for locally recurrent gastric neoplasms was 76% (35/46) to 87% (13/15)^[26,28]. In this study, the en bloc and curative resection rates of secondary ESD were 92.9% and 89.3%, respectively, which were comparable with those reported previously for secondary ESD. Two patients in the early salvage ESD group had no residual tumor. Although, they showed histological confirmation of positive lateral margins of the initial ESD specimen, no residual lesion was detected due to burning effects on the tissue by electrosurgical unit.

Early and late salvage ESD, which were both performed after histological confirmation of positive lateral margins of the primary ESD specimen, did not involve en bloc resection of the primary lesion. Therefore, the risks of local recurrence and lymph node metastasis resulting from piecemeal resection were always taken into consideration. Hence, careful surveillance after early and late salvage ESD is also very important. In this study, there was no local recurrence during the mean follow-up period in any patient who received secondary ESD.

There is no consensus on the timing of salvage ESD. Until now, there were few reports about the feasibility and effectiveness of early salvage ESD^[6,26,31]. In this study, we compared the clinicopathologic factors between early salvage ESD and late salvage ESD and found no significant differences in procedure or oncologic outcomes. However, further study about the timing of salvage ESD will be needed.

Although this study was retrospective with a small number of patients, this is the first study to report the feasibility and safety of secondary ESD according to the timing of ESD.

In conclusion, we found that secondary ESD appears to be a feasible and curative treatment. When we consider the morbidity of gastrectomy, secondary ESD of residual or locally recurrent gastric neoplasms is a good therapeutic option worth pursuing, although the procedure time is longer and associated with higher technical difficulty.

ARTICLE HIGHLIGHTS

Research background

Endoscopic submucosal dissection (ESD) is an accepted curative treatment option for gastric tumors with very low local recurrence. However, residual or locally recurrent tumors occur rarely after ESD. Although secondary ESD is technically demanding, it can be applied to residual or recurrent tumors with scar and dense fibrotic submucosa. We investigated the feasibility and safety of secondary ESD for gastric tumors. We also categorized secondary ESD into three groups according to the surgical strategy (early salvage, late salvage, or

late secondary ESD) and analyzed them.

Research motivation

There is no consensus on the timing of salvage ESD. Until now, there were few reports about the feasibility and effectiveness of early salvage ESD.

Research objectives

To investigate the feasibility and safety of secondary ESD for residual or locally recurrent gastric tumors.

Research methods

Between 2010 and 2017, 1623 consecutive patients underwent ESD for gastric neoplasms at a single tertiary referral center. Among these, 28 patients underwent secondary ESD for a residual or locally recurrent tumor. Our analysis compared clinicopathologic factors between primary ESD and secondary ESD groups.

Research results

The en bloc resection and curative rate of resection of secondary ESD were 92.9% and 89.3%. The average procedure time of secondary ESD was significantly longer than primary ESD, and the adverse events rate was not statistically different but trended slightly higher in the secondary ESD group compared to the primary ESD group. Patients who received secondary ESD had favorable outcomes without severe adverse events. During a mean follow-up period, no local recurrence occurred in patients who received secondary ESD.

Research conclusions

Although it requires greater technical efficiency and longer procedure time, secondary ESD of residual or locally recurrent gastric tumors appears to be feasible and curative treatment.

Research perspectives

Secondary ESD of residual or locally recurrent gastric tumors is a feasible and curative treatment.

REFERENCES

- Hoteya S, Iizuka T, Kikuchi D, Yahagi N. Benefits of endoscopic submucosal dissection according to size and location of gastric neoplasm, compared with conventional mucosal resection. *J Gastroenterol Hepatol* 2009; **24**: 1102-1106 [PMID: 19383079 DOI: 10.1111/j.1440-1746.2009.05811.x]
- Tanaka M, Ono H, Hasuiki N, Takizawa K. Endoscopic submucosal dissection of early gastric cancer. *Digestion* 2008; **77** Suppl 1: 23-28 [PMID: 18204258 DOI: 10.1159/000111484]
- Otsuka Y, Niwa Y, Ohmiya N, Ando N, Ohashi A, Hirooka Y, Goto H. Usefulness of magnifying endoscopy in the diagnosis of early gastric cancer. *Endoscopy* 2004; **36**: 165-169 [PMID: 14765314 DOI: 10.1055/s-2004-814184]
- Zhao Z, Yin Z, Wang S, Wang J, Bai B, Qiu Z, Zhao Q. Meta-analysis: The diagnostic efficacy of chromoendoscopy for early gastric cancer and premalignant gastric lesions. *J Gastroenterol Hepatol* 2016; **31**: 1539-1545 [PMID: 26860924 DOI: 10.1111/jgh.13313]
- Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2014 (ver. 4). *Gastric Cancer* 2017; **20**: 1-19 [PMID: 27342689 DOI: 10.1007/s10120-016-0622-4]
- Bae SY, Jang TH, Min BH, Lee JH, Rhee PL, Rhee JC, Kim JJ. Early additional endoscopic submucosal dissection in patients with positive lateral resection margins after initial endoscopic submucosal dissection for early gastric cancer. *Gastrointest Endosc* 2012; **75**: 432-436 [PMID: 22248614 DOI: 10.1016/j.gie.2011.09.044]
- Oka S, Tanaka S, Kaneko I, Mouri R, Hirata M, Kanao H, Kawamura T, Yoshida S, Yoshihara M, Chayama K. Endoscopic submucosal dissection for residual/local recurrence of early gastric cancer after endoscopic mucosal resection. *Endoscopy* 2006; **38**: 996-1000 [PMID: 17058164 DOI: 10.1055/s-2006-944780]
- Sekiguchi M, Suzuki H, Oda I, Abe S, Nonaka S, Yoshinaga S, Taniguchi H, Sekine S, Kushima R, Saito Y. Favorable long-term outcomes of endoscopic submucosal dissection for locally recurrent early gastric cancer after endoscopic resection. *Endoscopy* 2013; **45**: 708-713 [PMID: 23918620 DOI: 10.1055/s-0033-1344332]
- Yamamoto H, Kawata H, Sunada K, Sasaki A, Nakazawa K, Miyata T, Sekine Y, Yano T, Satoh K, Ido K, Sugano K. Successful en-bloc resection of large superficial tumors in the stomach and colon using sodium hyaluronate and small-caliber-tip transparent hood. *Endoscopy* 2003; **35**: 690-694 [PMID: 12929067 DOI: 10.1055/s-2003-41516]
- Chung IK, Lee JH, Lee SH, Kim SJ, Cho JY, Cho WY, Hwangbo Y, Keum BR, Park JJ, Chun HJ, Kim HJ, Kim JJ, Ji SR, Seol SY. Therapeutic outcomes in 1000 cases of endoscopic submucosal dissection for early gastric neoplasms: Korean ESD Study Group multicenter study. *Gastrointest Endosc* 2009; **69**: 1228-1235 [PMID: 19249769 DOI: 10.1016/j.gie.2008.09.027]
- Akasaka T, Nishida T, Tsutsui S, Michida T, Yamada T, Ogiyama H, Kitamura S, Ichiba M, Komori M, Nishiyama O, Nakanishi F, Zushi S, Nishihara A, Iijima H, Tsujii M, Hayashi N. Short-term outcomes of endoscopic submucosal dissection (ESD) for early gastric neoplasm: multicenter survey by osaka university ESD study group. *Dig Endosc* 2011; **23**: 73-77 [PMID: 21198921 DOI: 10.1111/j.1443-1661.2010.01062.x]
- Ahn JY, Jung HY, Choi KD, Choi JY, Kim MY, Lee JH, Choi KS, Kim DH, Song HJ, Lee GH, Kim JH, Park YS. Endoscopic and oncologic outcomes after endoscopic resection for early gastric cancer: 1370 cases of absolute and extended indications. *Gastrointest Endosc* 2011; **74**: 485-493 [PMID: 21741645 DOI: 10.1016/j.gie.2011.04.038]
- Shin KY, Jeon SW, Cho KB, Park KS, Kim ES, Park CK, Chung YJ, Kwon JG, Jung JT, Kim EY, Kim KO, Jang BI, Lee SH, Park JB, Yang CH. Clinical outcomes of the endoscopic submucosal dissection of early gastric cancer are comparable between absolute and new expanded criteria. *Gut Liver* 2015; **9**: 181-187 [PMID: 25167797 DOI: 10.5009/gnl13417]
- Nakamura K, Honda K, Akahoshi K, Ihara E, Matsuzaka H, Sumida Y, Yoshimura D, Akiho H, Motomura Y, Iwasa T, Komori K, Chijiwa Y, Harada N, Ochiai T, Oya M, Oda Y, Takayanagi R. Suitability of the expanded indication criteria for the treatment of early gastric cancer by endoscopic submucosal dissection: Japanese multicenter large-scale retrospective analysis of short- and long-term outcomes. *Scand J Gastroenterol* 2015; **50**: 413-422 [PMID: 25635364 DOI: 10.3109/00365521.2014.940377]
- Takenaka R, Kawahara Y, Okada H, Hori K, Inoue M, Kawano S, Tanioka D, Tsuzuki T, Yagi S, Kato J, Uemura M, Ohara N, Yoshino T, Imagawa A, Fujiki S, Takata R, Yamamoto K. Risk factors associated with local recurrence of early gastric cancers after endoscopic submucosal dissection. *Gastrointest Endosc* 2008; **68**: 887-894 [PMID: 18565523 DOI: 10.1016/j.gie.2008.03.1089]
- Oka S, Tanaka S, Kaneko I, Mouri R, Hirata M, Kawamura T, Yoshihara M, Chayama K. Advantage of endoscopic submucosal dissection compared with EMR for early gastric cancer. *Gastrointest Endosc* 2006; **64**: 877-883 [PMID: 17140890 DOI: 10.1016/j.gie.2006.03.932]
- Oda I, Saito D, Tada M, Iishi H, Tanabe S, Oyama T, Doi T, Otani Y, Fujisaki J, Ajioka Y, Hamada T, Inoue H, Gotoda T, Yoshida S. A multicenter retrospective study of endoscopic resection for early gastric cancer. *Gastric Cancer* 2006; **9**: 262-270 [PMID: 17235627 DOI: 10.1007/s10120-006-0389-0]
- Isomoto H, Shikuwa S, Yamaguchi N, Fukuda E, Ikeda K, Nishiyama H, Ohnita K, Mizuta Y, Shiozawa J, Kohno S. Endoscopic submucosal dissection for early gastric cancer: a large-scale feasibility study. *Gut* 2009; **58**: 331-336 [PMID: 19001058 DOI: 10.1136/gut.2008.165381]
- Goto O, Fujishiro M, Kodashima S, Ono S, Omata M. Outcomes of endoscopic submucosal dissection for early gastric cancer

- with special reference to validation for curability criteria. *Endoscopy* 2009; **41**: 118-122 [PMID: 19214889 DOI: 10.1055/s-0028-1119452]
- 20 **Kang HY**, Kim SG, Kim JS, Jung HC, Song IS. Clinical outcomes of endoscopic submucosal dissection for undifferentiated early gastric cancer. *Surg Endosc* 2010; **24**: 509-516 [PMID: 19585066 DOI: 10.1007/s00464-009-0614-0]
 - 21 **Nakamoto S**, Sakai Y, Kasanuki J, Kondo F, Ooka Y, Kato K, Arai M, Suzuki T, Matsumura T, Bekku D, Ito K, Tanaka T, Yokosuka O. Indications for the use of endoscopic mucosal resection for early gastric cancer in Japan: a comparative study with endoscopic submucosal dissection. *Endoscopy* 2009; **41**: 746-750 [PMID: 19681023 DOI: 10.1055/s-0029-1215010]
 - 22 **Tanabe S**, Ishido K, Higuchi K, Sasaki T, Katada C, Azuma M, Naruke A, Kim M, Koizumi W. Long-term outcomes of endoscopic submucosal dissection for early gastric cancer: a retrospective comparison with conventional endoscopic resection in a single center. *Gastric Cancer* 2014; **17**: 130-136 [PMID: 23576197 DOI: 10.1007/s10120-013-0241-2]
 - 23 **Park JC**, Lee SK, Seo JH, Kim YJ, Chung H, Shin SK, Lee YC. Predictive factors for local recurrence after endoscopic resection for early gastric cancer: long-term clinical outcome in a single-center experience. *Surg Endosc* 2010; **24**: 2842-2849 [PMID: 20428894 DOI: 10.1007/s00464-010-1060-8]
 - 24 **Onozato Y**, Ishihara H, Iizuka H, Sohara N, Kakizaki S, Okamura S, Mori M. Endoscopic submucosal dissection for early gastric cancers and large flat adenomas. *Endoscopy* 2006; **38**: 980-986 [PMID: 17058161 DOI: 10.1055/s-2006-944809]
 - 25 **Kakushima N**, Fujishiro M, Kodashima S, Kobayashi K, Tateishi A, Iguchi M, Imagawa A, Motoi T, Yahagi N, Omata M. Histopathologic characteristics of gastric ulcers created by endoscopic submucosal dissection. *Endoscopy* 2006; **38**: 412-415 [PMID: 16680644 DOI: 10.1055/s-2006-925166]
 - 26 **Hoteya S**, Iizuka T, Kikuchi D, Mitani T, Matsui A, Ogawa O, Furuhashi T, Yamashita S, Yamada A, Kaise M, Yahagi N. Secondary endoscopic submucosal dissection for residual or recurrent tumors after gastric endoscopic submucosal dissection. *Gastric Cancer* 2014; **17**: 697-702 [PMID: 24310295 DOI: 10.1007/s10120-013-0325-z]
 - 27 **Shimamura Y**, Ishii N, Nakano K, Ikeya T, Nakamura K, Takagi K, Fukuda K, Suzuki K, Fujita Y. Repeat endoscopic submucosal dissection for recurrent gastric cancers after endoscopic submucosal dissection. *World J Gastrointest Endosc* 2013; **5**: 600-604 [PMID: 24368936 DOI: 10.4253/wjge.v5.i12.600]
 - 28 **Yokoi C**, Gotoda T, Hamanaka H, Oda I. Endoscopic submucosal dissection allows curative resection of locally recurrent early gastric cancer after prior endoscopic mucosal resection. *Gastrointest Endosc* 2006; **64**: 212-218 [PMID: 16860071 DOI: 10.1016/j.gie.2005.10.038]
 - 29 **Okada K**, Fujisaki J, Kasuga A, Omae M, Yoshimoto K, Hirasawa T, Ishiyama A, Yamamoto Y, Tsuchida T, Hoshino E, Igarashi M, Takahashi H. Endoscopic ultrasonography is valuable for identifying early gastric cancers meeting expanded-indication criteria for endoscopic submucosal dissection. *Surg Endosc* 2011; **25**: 841-848 [PMID: 20734082 DOI: 10.1007/s00464-010-1279-4]
 - 30 **Higashimaya M**, Oka S, Tanaka S, Numata N, Sanomura Y, Yoshida S, Arihiro K, Chayama K. Endoscopic submucosal dissection for residual early gastric cancer after endoscopic submucosal dissection. *Gastrointest Endosc* 2013; **77**: 298-302 [PMID: 23206812 DOI: 10.1016/j.gie.2012.09.003]
 - 31 **Kikuchi D**, Iizuka T, Hoteya S, Yamada A, Furuhashi T, Yamashita S, Domon K, Nakamura M, Matsui A, Mitani T, Ogawa O, Watanabe S, Yahagi N, Kaise M. Safety and efficacy of secondary endoscopic submucosal dissection for residual gastric carcinoma after primary endoscopic submucosal dissection. *Digestion* 2012; **86**: 288-293 [PMID: 23051712 DOI: 10.1159/000342114]

P- Reviewer: Akiho H, Nishida T **S- Editor:** Wang XJ
L- Editor: Filipodia **E- Editor:** Huang Y





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ISSN 1007-9327

